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Bisphenol A and Puberty Onset in Female Mice: Developmental Effects of Low-Dose Exposure

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Endocrine-disrupting chemicals, such as the plasticizer bisphenol A (BPA), may perturb the timing of human puberty.[1,2] A study in *Environmental Health Perspectives*[3] demonstrates that even low doses of BPA accelerate puberty onset in female mice and identifies potential mechanisms that may explain this observation.

Peptides such as neurokinin B (NKB) and the family of kisspeptins are essential regulators of puberty in rodents and humans.[4] In mice, the *Kiss1* gene is expressed in the neurons of two adjacent, functionally distinct hypothalamic regions: the rostral periventricular region of the third ventricle (RP3V) and the arcuate nucleus (ARC).[5,6] ARC neurons also express *Tac2*, which encodes NKB.[7]

As part of the hypothalamic–pituitary–gonadal axis, the Kiss1/NKB system controls the production of gonadotropin-releasing hormone. This molecular switch stimulates the pituitary gland to secrete gonadotropins, which regulate the production of sperm and egg follicles.[6] The ARC neurons likely play a broader role in regulating puberty, while the RP3V neurons also control ovulation after sexual maturation.[4,8]

Improvements in nutrition likely explain some of the observed decrease in the average age at menarche between 1890 and 1960 in Europe and the United States.[9] However, secular changes in puberty onset are complex. Childhood obesity may explain some but not all of the trend toward earlier breast development in girls,[10] while the distribution of menarcheal age has shifted toward lateness in some populations.[9] Similar divergent effects on initial and final pubertal stages have been observed in boys.[1] This suggests a contribution of environmental factors, perhaps including BPA exposure from food and beverage containers, toys, and office products.[11,12] BPA's ability to disrupt the kisspeptin system supports this hypothesis.[13,14]

The new study is an international collaboration directed by Manuel Tena-Sempere at the University of Córdoba, Spain, and GianCarlo Panzica at the University of Torino, Italy. "Given previous findings, we wanted to study the effect of low-dose perinatal BPA exposure on vaginal opening, a phenotypic marker of puberty onset in female mice," says Tena-Sempere. "We also wanted to correlate this phenotypic effect with changes in the Kiss1/NKB system at the level of mRNA and protein."

For their study, the research team exposed four groups of 10 pregnant mice to vehicle (control) or three different doses of BPA. All orally administered BPA doses (5, 10, and 40 μg/kg per day) were below current human safety levels set by European and U.S. regulatory agencies. From the female offspring of the 40 litters, the researchers collected vaginal opening data and blood and brain samples at multiple time points for hormone measurements, gene expression, and protein analysis.

Compared with controls, all three exposed groups had a significantly earlier age of vaginal opening. Similar to other BPA studies,[15,16] the lowest and highest exposure levels had similar outcomes while the effect of the intermediate dose was less pronounced.

BPA reduced circulating levels of gonadotropins and had divergent effects on the two neuronal populations. Although effects varied somewhat by age, all three exposure levels resulted in more kisspeptin neurons in the RP3V but lower kisspeptin immunoreactivity in the ARC. Reduced *Kiss1* and *Tac2* gene expression levels were also observed in the ARC. These distinct effects on important regulators of sexual maturation might explain why BPA advances some manifestations of puberty while delaying others, says Tena-Sempere.

Panzica notes a positive feedback of RP3V neurons to estrogens in physiological conditions, in contrast to a negative feedback for ARC neurons.[17] The underlying mechanism may involve progesterone signaling.[18] "Present results indicate that this differential sensitivity is probably established early during the development

Girls have been entering puberty at increasingly younger average ages since the 1800s, in no small part because health and nutrition have improved over time.[20] Today, environmental factors, perhaps including endocrine disruptors, may influence the onset of puberty in complex ways. © iStockphoto/Shanina; © iStockphoto/George Marks; © iStockphoto/lcodacci; © iStockphoto/Alex Potemkin.

and this may explain the different effects of BPA on the two hypothalamic nuclei," Panzica says.

For Anne-Simone Parent, an associate professor of pediatric endocrinology at the University of Liège in Belgium, the new study has multiple strengths. "The BPA doses mimic human exposure, and the comprehensive analysis illustrates the exquisite sensitivity of the Kiss1/NKB system to endocrine disruptors," says Parent, who was not involved in the work. "Detecting brain region–specific BPA effects is a novel contribution and a potential explanation for the abnormal programming of puberty."

The distribution of pubertal onset, Parent adds, is an important marker of reproductive health at the population level. For individuals, puberty disruptions may have downstream effects, such as irregular estrous cycles and compromised adult fertility.[19]

For Heather Patisaul, a professor of biological sciences at North Carolina State University who also was not involved in the research, the study offers compelling evidence that even low doses of BPA may have significant effects on puberty in girls. "To me, it is becoming unavoidably obvious that our environment is changing the human trajectory, including the timing of sexual maturation," Patisaul says. "A key strength of this paper is its mechanistic focus, which elegantly addresses the 'why' question."

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